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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,966	09/15/2003	Marioara Mendelovici	1662/579021	1081

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KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 03/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,966	MENDELOVICI ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-31* is/are rejected.

7)☒ Claim(s) *28-31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/15/03, 8/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: English translation of JP 6377057

DETAILED ACTION

Claims 28-31 are currently pending in the instant application and are objected and rejected.

Election/Restrictions

Applicant's election with traverse of Group II, claims 29-31, drawn to the crystalline sodium salt form of benzisoxazole methane sulfonic acid, in the reply filed on 6 December 2005 is acknowledged. The traversal is on the ground(s) that there is no undue burden to search all of the groups. This is not found persuasive because the inventions are independent and distinct because there is no patentable co-action between the groups and a reference anticipating one member will not render another obvious. Each group is directed to art recognized divergent subject matter, which require different searching strategies for each group. Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner.

Applicants' instant claim 28 is drawn to a crystalline form of benzisoxazole methane sulfonic acid, which includes in the form an acid form and a salt form. Therefore, in addition to claims 29-31 drawn to the crystalline sodium salt form of benzisoxazole methane sulfonic acid, the examiner will also include claim 28, drawn to the crystalline sodium salt form of benzisoxazole methane sulfonic acid, in the elected invention.

Therefore, **the elected invention for search and examination is** the crystalline sodium salt form of benzisoxazole methane sulfonic acid of claims 28-31.

The remaining subject matter of claims 28-31 that is not drawn to the above elected invention for search and examination, i.e. the subject matter that is not drawn to the crystalline sodium salt form of benzisoxazole methane sulfonic acid, is withdrawn under 37 CFR 1.142(b) as being for non-elected subject matter. The remaining compounds which are not within the elected invention, which are independent and distinct from the elected invention and do not have unity with the elected compound and are therefore withdrawn by means of a restriction requirement within the claims are, for example, the crystalline acid form of benzisoxazole methane sulfonic acid, the crystalline calcium salt, barium salt, potassium salt, magnesium salt, lithium salt, manganese salt, cobalt salt, iron salt, copper salt, nickel salt, zinc salt and silver salt form of benzisoxazole methane sulfonic acid.

The requirement is still deemed proper.

Claim Objections

Claims 28-31 are objected to as containing non-elected subject matter, i.e. subject matter other than the elected invention of the crystalline sodium salt form of benzisoxazole methane sulfonic acid. Claims 28-31 presented drawn solely to the elected invention would overcome this objection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-4 and 10-12 of copending Application No. 10/288135 (US Pre Grant Publication 20030144527). Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are claiming a crystalline sodium salt of

benzisoxazole methane sulfonic acid of Form IV with the specific x-ray diffraction data as found in conflicting claim 2. Conflicting claims 2-4 and 10-12 of copending Application No. 10/288135 anticipate applicants' instant claims 28-31 and are therefore considered as obvious type double patenting as the crystalline sodium salt of benzisoxazole methane sulfonic acid of Form IV found in the conflicting claims is a species within applicants' instantly claimed crystalline sodium salt form of benzisoxazole methane sulfonic acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. However, it is noted that copending Application No. 10/288135 will mature into US Patent No. 7,015,330 on March 21, 2006.

Claims 28-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 38-43 of copending Application No. 10/662986 (US Pre Grant Publication 20040138472). Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are claiming a crystalline sodium salt of benzisoxazole methane sulfonic acid of Form II (which defined in the specification of 10/662986 has the properties as found on page 20 and also as claimed in conflicting claims 39-43). Conflicting claims 38-43 of copending Application No. 10/662986 anticipate applicants' instant claims 28-31 and are therefore considered as obvious type double patenting as the crystalline sodium salt of benzisoxazole methane sulfonic acid of Form II found in the conflicting claims is a species within applicants' instantly claimed crystalline sodium salt form of benzisoxazole methane sulfonic acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 28-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 32-37, 44-48 and 49-52 of copending Application No. 10/928313 (US Pre Grant Publication 20050027126). Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are claiming a crystalline sodium salt of benzisoxazole methane sulfonic acid of Form I (conflicting claims 32-37), Form III (conflicting claims 44-48), and Form V (conflicting claims 49-52). Conflicting claims 32-37, 44-48 and 49-52 of copending Application No. 10/928313 anticipate applicants' instant claims 28-31 and are therefore considered as obvious type double patenting as they crystalline sodium salt of benzisoxazole methane sulfonic acid of Form I, Form III and Form V found in the conflicting claims are species within applicants' instantly claimed crystalline sodium salt form of benzisoxazole methane sulfonic acid.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28-31 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 4,172,896. US Patent No. 4,172,896 discloses solid crystalline compounds of the same chemical structure. Specifically the reference discloses BOS-Na compounds of the formula (V), column 3, which is a crystalline compound, see example

1 (column 7, lines 11-14) which discloses crystalline sodium 1,2-benzisoxazole-3-methanesulfonate.

Claims 28-31 are rejected under 35 U.S.C. 102(b) as being anticipated by FR 2428033. FR 2428033 discloses solid crystalline compounds of the same chemical structure. Specifically the reference discloses BOS-Na compounds of the formula V, page 4, which is a crystalline compound, see example 1 (column 8, lines 28-30) which discloses crystalline sodium 1,2-benzisoxazole-3-methanesulfonate.

Claims 28-31 are rejected under 35 USC 102(b) as being anticipated by JP 53077057. *(Note: The page numbers cited below are from the English translation of JP 53-77057 which is being sent with this office action.)*

JP 53077057 discloses solid crystalline compounds of the same chemical structure. Specifically the reference discloses the sodium salt of 1,2-benzisoxazole-3-methane sulfonic acid on page 10, which is a crystal, see lines 7-8.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 28-31 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,677,458.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

US Patent No. 6,677,458 discloses solid compounds of the same chemical structure. Specifically, the reference discloses BOS-Na on column 3, lines 20 and 39-41, which is isolated as sodium salt by evaporation of the aqueous layer and on column 4, lines 42-49, which is isolated by precipitation from an aqueous solution.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 1, 2006

Rebecca Anderson
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

PTO 04-0486

CY=JA DATE=19780708 KIND=A
PN=53-077057

1,2-BENZISOXAZOLE DERIVATIVES
[1,2-BENZUISOKISAZO-RU YUDOTAI]

Hitoshi Uno, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. November 2003

Translated by: FLS, Inc.

PUBLICATION COUNTRY	(19):	JP
DOCUMENT NUMBER	(11):	53077057
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PUBLICATION DATE	(43):	19780708
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APPLICATION DATE	(22):	19761216
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INTERNATIONAL CLASSIFICATION	(51):	
DOMESTIC CLASSIFICATION	(52):	C07D 261/20; C07D 413/12; //A61K 31/41; A61K 31/495; (C07D 413/12; C07D 261/20; C07D 295/00
PRIORITY COUNTRY	(33):	
PRIORITY NUMBER	(31):	
PRIORITY DATE	(32):	
INVENTOR	(72):	UNO; HIROSHI, ET AL.
APPLICANT	(71):	DAINIPPON PHARMACEUTICAL CO., LTD.
TITLE	(54):	1,2-BENZISOXAZOLE DERIVATIVES
FOREIGN TITLE	[54A]:	1,2-BENZUISOKISAZO-RU YUDOTAI

Specifications

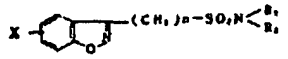
/441*

1. Title of the Invention

1,2-Benzisoxazole Derivatives

2. Claim(s)

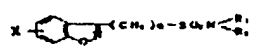
1) A compound represented by the general formula:



(where **X** in the formula means a hydrogen atom, halogen atom or trifluoromethyl group; R_1 and R_2 mean the same or different hydrogen atom, 1 to 3 carbon straight or branched chain lower alkyl group or hydroxyl group (except when R_1 and R_2 each are a hydroxyl group), or $-N<^{R_1}_{R_2}$ means a 4-methyl-1-piperazinyl group; **n** means an integer from 1 to 3).

2) An alkali metal salt of the compound of claim 1 wherein R_1 and/or R_2 is a hydrogen atom.

3) The compound of claim 1 represented by the general formula:



(Where **X** in the formula means a hydrogen atom or 5th or 6th halogen atom; R_1 and R_2 mean the same or different hydrogen atom, and a methyl, ethyl, isopropyl or hydroxyl group (except when R_1 and R_2 each are a hydroxyl group), or $-N<^{R_1}_{R_2}$ means a 4-methyl-1-piperazinyl group; and **n** means an integer from 1 to 3).

4) The compound of claim 3 wherein R_1 and R_2 each are a hydrogen atom.

5) The compound of claim 3 wherein $-N<^{R_1}_{R_2}$ is a methylamino group, ethylamino group, isopropylamino group, dimethylamino group, hydroxyamino

*Number in the margin indicates pagination in the foreign text.

group or 4-methyl-1-piperazinyl group; and **n** is 1.

6) The compound of claim 4 where **n** is 1. /442

7) The compound of claim 6 which is 3-sulfoamoylmethyl-1,2-benzisoxazole.

8) The compound of claim 6 which is 5-fluoro-3-sulfoamoylmethyl-1,2-benzisoxazole.

9) The compound of claim 6 which is 5-chloro-3-sulfoamoylmethyl-1,2-benzisoxazole.

10) The compound of claim 6 which is 5-bromo-3-sulfoamoylmethyl-1,2-benzisoxazole.

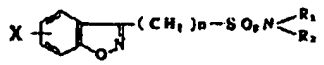
11) The compound of claim 6 which is 6-fluoro-3-sulfoamoylmethyl-1,2-benzisoxazole.

12) The alkali metal salt of claim 2 which is a 3-sulfamoylmethyl-1,2-benzisoxazole sodium salt.

13) The alkali metal salt of claim 2 which is a 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole sodium salt.

3. Detailed Specifications

The present invention relates to novel and useful 1,2-benzisoxazole derivatives, and in further detail, 3-sulfamoylalkyl-1,2-benzisoxazole derivatives represented by the general formula (I):



(I)

(where **X** in the formula means a hydrogen atom, halogen atom or trifluoromethyl group; R_1 and R_2 mean the same or different hydrogen atom, 1 to 3 carbon straight or branched chain lower alkyl group or hydroxyl group (except

when R_1 and R_2 each are a hydroxyl group), or $-N<^{R_1}_{R_2}$ means a 4-methyl-1-piperazinyl group; and **n** means an integer from 1 to 3), an alkali metal salt thereof when R_1 and/or R_2 is a hydrogen atom, and a method for manufacturing these compounds.

Fluorine, chlorine and bromine atoms are cited as specific examples of the halogen atom represented by **X** in the above-mentioned formula.

The inventors of the present invention researched various 1,2-benzisoxazole derivatives, but by introducing a 3rd sulfamoylalkyl group, they discovered that an excellent antiepileptic action was expressed, and they achieved the present invention as a result the painstaking research.

The preferred compound out of the compounds of the present invention is a compound wherein **X** in formula (I) is a hydrogen atom or 5th or 6th halogen atom; R_1 and R_2 are methyl, ethyl, isopropyl or hydroxyl groups (except when R_1 and R_2 each are a hydroxyl group), or $-N<^{R_1}_{R_2}$ is a 4-methyl-1-piperazinyl group; and **n** is an integer from 1 to 3.

Another preferred compound wherein **X** in formula (I) is a hydrogen atom or a 5th or 6th halogen atom; R_1 and R_2 are each a hydrogen atom; **n** is an integer from 1 to 3; and **X** is the same as in the previous case; $-N<^{R_1}_{R_2}$ is a methylamino, ethylamino, isopropylamino, dimethylamino, hydroxyamino or 4-methyl-1-piperazinyl group; and **n** is 1.

The most preferred compound is a compound wherein **X** in formula (I) is a hydrogen atom or 5th or 6th halogen atom; R_1 and R_2 are each a hydrogen atom; and **n** is 1. The two aforesaid compounds are especially preferred even though the following compounds are cited as examples:

3-sulfamoylmethyl-1,2-benzisoxazole,

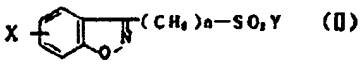
5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole,

5-chloro-3-sulfamoylmethyl-1,2-benzisoxazole,

5-bromo-3-sulfoamoylmethyl-1,2-benzisoxazole, /443

6-fluoro-3-sulfoamoylmethyl-1,2-benzisoxazole.

The compound (I) of the present invention is obtained by allowing the compound represented by the general formula (II):



(II)

(Where **X** and **n** in the formula mean the same compounds as stated above and **Y** means a halogen atom.)

and an amine represented by the general formula (III):

(III)

(Where R_1 and R_2 mean the same compounds as stated above.)

to react.

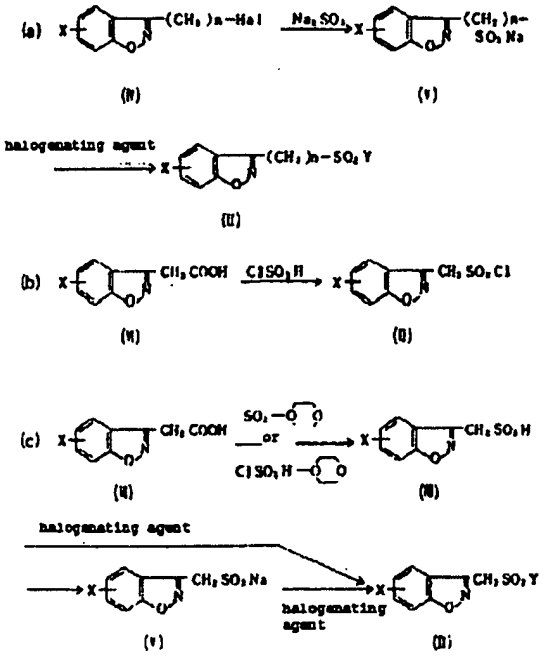
The reaction between the compound (II) and amine (III) may be performed without a solvent or in an inactive solvent, but it is preferably performed in an inactive solvent. Water, an alcohol, such as ethanol or isopropanol; an aromatic hydrocarbon, such as toluene or xylene; an ether, such as diethyl ether, tetrahydrofuran or dioxane; and an ester, such as ethyl acetate, are cited as examples of the inactive solvent, but an ether or ester is especially preferred. These respective solvents can be used alone or by mixing two or more of them.

This reaction is preferably performed in the presence of a basic substance as a dehydrohalogenating agent. An alkali bicarbonate, such

as sodium bicarbonate or potassium bicarbonate; an alkali carbonate, such as sodium carbonate or potassium carbonate; or an organic base, such as triethylamine, are cited as examples of the basic substance. Moreover, the dehydrohalogenating agent per se can be used therewith by using an excessive amount of the amine (III).

The amount of the amine (III) is an equimolar amount or four 4 times the molar amount of the usual amount of compound (II), but an overexcessive amount can be used as well. The reaction temperature is not particularly limited, but it is preferably 0°C or 35°C.

The raw material compound (II) may be manufactured in, e.g., the following methods:



(Where **X**, **Y** and **n** mean the same compounds as stated above and **Hal** means a halogen atom.)

According to the method (a), a sodium 3-alkylsulfonate derivative (V) is obtained by allowing a 3-halogenoalkylated compound (IV) (synthesized

according to the method described in Chem. Pharm. Bull (Tokyo) 24 (1976):632) and sodium sulfite to react in an inactive solvent (e.g., aqueous methanol, aqueous ethanol) at 40 to 80°C, and then the compound (II) can be obtained by allowing this to react with a halogenating agent (e.g., phosphorus oxychloride, phosphorus oxybromide).

The compound in formula (II) where **n** is 1 is also obtained in method (b) or (c).

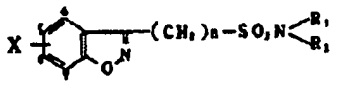
According to method (b), a chloride (II) of 3-methane sulfonic acid can be obtained by allowing 3-acetic acid (VI) (synthesized according to the method described in Phytochemistry 10 (1971):539) to react with chlorosulfonic acid without a solvent at 50 to 70°C.

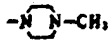
According to method (c), 3-methane sulfonic acid (VII) is obtained by allowing the 3-acetic acid (VI) to react with anhydrous sulfuric acid and dioxane (J. Am. Chem. Soc. 75 (1953):1651)) or chlorosulfonic acid and dioxane in an inactive solvent (e.g., ethylene chloride, /444 chloroform) at 35 to 70°C, and then a chloride of 3-methane sulfonic acid (II) can be obtained by acting a halogenating agent on this, based on the sodium salt (V), or acting a halogenating agent directly on 3-methane sulfonic acid (VII).

The compounds of the present invention where R_1 and/or R_2 is a hydrogen atom in formula (I) can be derived into alkali metal salts by allowing them to react with alkali metal compounds in the usual method. Alkali hydroxides, such as sodium hydroxide or potassium hydroxide; or alkali metal alcoholates, such as sodium ethylate, are cited for the alkali metal compound used here.

The compounds (I) of the present invention or their alkali metal salts exhibit antiepileptic action, so they are useful as, e.g., antiepileptics. The anti-maximal electric shock action (anti-MES action; measured according to the method described in J. Am. Pharm. Assoc. 38 (1949):201) on mice of the compounds (I) of the present invention are as shown in Table 1.

Table 1. Anti-Maximal Electric Shock Action on Mice



Test Compound			ED_{50} (mg/kg) (p.o.)	Test Compound			ED_{50} (mg/kg) (p.o.)
n	X	$-N<^{R_1}_{R_2}$		n	X	$-N<^{R_1}_{R_2}$	
1	H	$-NH_2$	19.6	1	5-F	$-NHCH_3$	34.5
1	H	$-NHCH_3$	22.3	1	5-F	$-NHC_2H_5$	31.6
1	H	$-NHC_2H_5$	38.9	1	5-F	$-N(CH_3)_2$	32.0
1	H	$-NHCH(CH_3)_2$	56.0	1	5-Br	$-NH_2$	13.5
1	H	$-N(CH_3)_2$	37.2	1	5-Br	$-NHCH_3$	15.0
1	H		57.1	1	5-Br	$-NHC_2H_5$	18.3
1	H	$-NHOH$	32.4	1	5-Br	$-NHCH(CH_3)_2$	22.3
1	5-Cl	$-NH_2$	14.2	1	6-Br		87.7
1	5-Cl	$-NHCH_3$	約20	1	6-F	$-NH_2$	18.9
1	5-Cl	$-NHC_2H_5$	21.3	2	H	$-NH_2$	26.1
1	5-Cl	$-N(CH_3)_2$	56.2	3	H	$-NH_2$	38.9
1	5-F	$-NH_2$	14.5				
Primidone			21.7	Phenacemide			61.2

Moreover, the NTD_{50} (50 % neutrotoxic dose; measured in a rotarod method) on mice, LD_{50} (observed for seven 7 days; calculated out in Probit's method), therapeutic index (NTD_{50}/ED_{50} (anti-MES action)), and safety margin (LD_{50}/ED_{50} (anti-MES action) are as shown in Table 2.

Table 2 (Mouse, Oral)

Test compound	NTD_{50} (mg/kg)	Therapeutic index	LD_{50} (mg/kg)	Safety margin
Compound of Practical Example 1	292	14.9	1,829	93.3
Compound of Practical Example 2	154	10.6	1,257	86.7

When the compound (I) of the present invention and its alkali metal salt is used as antiepileptic alone or by mixing it with additives used for physiologically tolerated preparations in the form of solid preparations, such as tablets, capsules, fine powders and suppositories, or liquid preparations, such as syrups and injections, and these are administered orally or parenterally. The dosage of the compound (I) of the present invention and its alkali metal salts varies depending on the type of compound, method of administration, age, and the like, but it is usually 10 to 100 mg/kg/day, and preferably, 3 to 50 mg/kg/day.

The present invention will now be specifically described by citing reference examples and practical examples, but the present invention is not limited to these practical example. Moreover, identification of the compound was performed by elemental analysis, mass spectrometry, IR spectrometry, NMR spectrometry, etc.

Reference example 1

5-fluoro-1,2-benzisoxazole-3-methane sulfonic acid chloride

3.0 g 5-fluoro-1,2-benzisoxazole-3-acetic acid (melting point: 151 to 156°C) are added to 20 mL of chlorosulfonic acid and stirred for 5 hours at 60°C. The target compound is obtained by cooling the reactant and pouring it into ice water, which is filtered out and subsequently washed with a small amount of cold water to be used in the subsequent reaction.

Reference Example 2 /445

1,2-benzisoxazole-3-methane sulfonic acid chloride

A solution in which 8.0 g 3-bromomethyl-1,2-benzisoxazole (melting

point: 64 to 66°C) were dissolved in 130 mL methanol and 8.1 g sodium sulfite were dissolved in 130 mL is added therein. After heating and stirring the above-mentioned mixture for 4 hours at 50°C, it is concentrated under reduced pressure, 250 mL of methanol are added to the crystal residue, which is then heated and dissolved. After filtering out the undissolved impurities with methanol, the methanol is distilled under reduced pressure, and upon removing the crystal residue and washing it with ether, 10.5 g of a crude sodium salt of 1,2-benzisoxazole-3-methane sulfonic acid are obtained.

10.5 g of the above-mentioned sodium salt were added to 100 mL of phosphorus oxychloride and subjected to a heat reflux for 3 hours. The excess phosphorus oxychloride is filtered out under reduced pressure, then dried and hardened. This residue is dissolved in 200 mL of ethyl acetate, and the target ethyl acetate solution is obtained by filtering out the impurities.

Reference Example 3

1,2-benzisoxazole-3-methane sulfonic acid chloride

11.0 g chlorosulfonic acid are dissolved in 50 mL ethylene chloride, and 8.2 g dioxane are added dropwise under ice water at an internal temperature of 10 to 15°C. 15.0 g 1,2-benzisoxazole-3-acetic acid are then added and stirred for 3 hours at room temperature and then for 6 hours at 50°C. Next, cold water is added to the reactant, the aqueous layer is separated and this is neutralized with an aqueous sodium hydroxide solution. The aqueous layer is concentrated under reduced pressure, dried and hardened, 90 mL of phosphorus oxychloride are added to the residue, and reacted

and treated as in the last step in Reference Example 2 to obtain the target ethyl acetate solution compound.

Practical Example 1

3-sulfamoylmethyl-1,2-benzisoxazole

200 mL of the ethyl acetate solution of 1,2-benzisoxazole-3-methane sulfonic acid chloride (the solution obtained in Reference Example 2) are cooled in ice and saturated with ammonia gas. After setting this aside for 1 hour at room temperature, the undissolved substance in the ethyl acetate is filtered out and the ethyl acetate is distilled off. After washing the residue with a small amount of ethyl acetate, it is recrystallized with ethyl acetate to obtain 5.2 g of the target compound (melting point: 160 to 163°C).

Practical Example 2

5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole

50 mL of cold concentrated ammonia water are added to the 5-fluoro-1,2-benzisoxazole-3-methane sulfonic acid chloride obtained in Reference Example 1 and set aside for 1 hour at room temperature. The ammonia water is distilled off under reduced pressure, ethyl acetate is added to the residue, then heated to dissolve it. After filtering out the impurities, the filtrate is concentrated under reduced pressure and a crystal is deposited. The deposited crystal is filtered and washed with benzene to obtain 0.9 g of the target compound (melting point: 182 to 185°C).

Practical Example 3

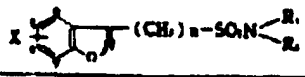
3-(4-methyl-1-piperazinyl)sulfonylmethyl-1,2-benzisoxazole

2.0 g of sodium 1,2-benzisoxazole-3-methane sulfonic acid are dissolved in 10 mL of phosphorus oxychloride and subjected to a heat reflux for 4 hours. The phosphorus oxychloride is distilled off under reduced pressure, the residue is dissolved in 50 mL of ether, and a solution in which 3 mL of 1-methylpiperazine were dissolved in 30 mL of ether under cooling is added and set aside for 30 minutes. This ether solution is washed with a 10 % sodium carbonate aqueous solution and water, dried with anhydrous sodium sulfate, and the ether is subsequently distilled off. Upon recrystallizing the residue with benzene/n-hexane, 0.6 g of the target compound are obtained (melting point: 119 to 121°C).

Practical Example 4

This subjected to a reaction and treated as in Practical Examples 1 to 3 to obtain the compounds in Table 3.

Table 3



n	X	$-N<^{R_1}_{R_2}$	Melting point (°C)
1	H	-NHCH$_3$	113 ~ 115
1	H	-NHCH$_2$CH$_3$	76 ~ 78
1	H	-NHCH$_2$CH$_2$CH$_3$	86 ~ 88
1	H	-NHCH(CH$_3$)$_2$	114 ~ 117
1	H	-N(CH$_3$)$_2$	105 ~ 107
1	H	-NHOH	140 ~ 143
1	5-F	-NHCH$_3$	141 ~ 144
1	5-F	-NHCH$_2$CH$_3$	114 ~ 117
1	5-F	-NHCH(CH$_3$)$_2$	127 ~ 130
1	5-F	-N(CH$_3$)$_2$	145 ~ 148
1	5-F		151 ~ 153
1	5-F	-NH$_2$	187 ~ 190
1	5-Cl	-NH$_2$	192 ~ 195
1	5-Cl	-NHCH$_3$	148 ~ 151
1	5-Cl	-NHCH$_2$CH$_3$	150 ~ 152

n	X	$-N<^{R_1}_{R_2}$	Melting point (°C)
1	5-Cl	-NHCH(CH$_3$)$_2$	114 ~ 116
1	5-Cl	-N(CH$_3$)$_2$	176 ~ 179
1	5-Br	-NH$_2$	221 ~ 225
1	5-Br	-NHCH$_3$	152 ~ 154
1	5-Br	-NHCH$_2$CH$_3$	144 ~ 147
1	5-Br	-NHCH(CH$_3$)$_2$	95 ~ 97
1	5-Br	-N(CH$_3$)$_2$	183 ~ 185
1	5-Br		118 ~ 121
2	H	-NH$_2$	159 ~ 162
3	H	-NH$_2$	136 ~ 138

Practical Example 5

3-sulfamoylmethyl-1,2-benzisoxazole sodium salt

A solution in which 7.0 g 3-sulfamoylmethyl-1,2-benzisoxazole were dissolved in 300 mL of ethanol and 0.76 g sodium were dissolved in 40

mL of ethanol is added, and after setting this aside for a brief period, the ethanol is distilled off under reduced pressure and the deposited crystal is filtered out, and upon washing it with ethanol, 6.5 g of the target compound are obtained (melting point: 225 to 230°C (decomposition).

This is subjected to the reaction and treatment as in the above-mentioned practical examples to obtain the following compound: 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole sodium salt (melting point: 240 to 243°C (decomposition))